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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,669	07/16/2003	Kathleen M. Hanley	LSBC-Hanley-0195	8535

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EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,669	HANLEY ET AL.	
	Examiner	Art Unit	
	David H. Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/6/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-26 and 28-34 in the reply filed on 10 July 2006 is acknowledged. The traversal is on the ground(s) that Group II, at least should be examined with Group I. This argument is found to be persuasive as it applies to Group II, directed to expressing an antisense element to reduce the amount of protein of interest cleaved by a hydrolase activity in a host cell. Applicants' cancellation of claims 27 and 35-37 renders the traversal moot as directed to Groups V-VII. The restriction of Groups III and IV is still deemed proper and made final.

2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR § 1.17(i).

Information Disclosure Statement

3. The listing of references in the specification on pages 57-63 is not a proper information disclosure statement. 37 CFR § 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

4. The IDS filed 6 August 2004 has been considered, a signed copy is attached hereto.

Drawings

5. New corrected drawings in compliance with 37 CFR § 1.121(d) are required in this application because Figures 4, 6, 10 and 11 are not in sequence compliance hence this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825: Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 23, line 2. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. The disclosure is objected to because of the following informalities:

SEQ ID NOs are missing on page 34, lines 24-32; page 35, line 24; Table 2, page 37; page 39, line 17; page 40, lines 12-20; table 3 on page 41; page 45, line 25.

Table 6 on page 54 is objected to because the specification does not contain a "Table 5".

Appropriate correction is required.

Claim Objections

8. Claim 2 is objected to as being directed to a non-elected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1-17 and 20-26 rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 and 20-26 are indefinite because it is unclear if the one or more polynucleotides are transgenes or inherent to the host cell, hence the metes and bounds of the claims are unclear.

At claim 10, "a Nicotianalisin protein" is indefinite because the term is not an art-defined limitation, and the phrase does not state the metes and bounds of the claimed invention.

At claim 14, "said first polynucleotide" lacks proper antecedent basis in claim 1.

Claims 15, 20 and 23 are indefinite because the limitation "inserted into a vector" is unclear, specifically whether Applicants are claiming a viral vector or if the claim is referring to the means by which the one or more polynucleotides was/were introduced into the host cell of claim 1. Hence, the metes and bounds of the claims are unclear.

Claim 25 is indefinite because it is unclear what "The plant cell comprising the plant cell" encompasses.

11. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 10 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a host cell with reduced protease activity comprising a polynucleotide that inhibits a subtilisin-like serine protease that is a Nicotianalisin, inhibited by a sense or antisense nucleotide sequence.

Applicant describes amino acid sequences for two Nicotianalisin proteins in SEQ ID NO: 24 and 25.

It is unclear from the instant specification if the entire genus of Nicotianalisin proteins is described in the instant Application, what percent identity is encompassed by the limitation Nicotianalisin proteins.

Hence, it is unclear that Applicant was in possession of the invention as broadly claimed. See also, MPEP § 2163 which states that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without

any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. See *Vas-Cath Inc. v. Mahurkar* 1991 (CA FC) 19 USPQ2d 1111, 1115, which teaches that the purpose of the written description is for the purpose of warning an innocent purchaser, or other person using a machine, of his infringement of the patent; and at the same time, of taking from the inventor the means of practicing upon the credulity or the fears of other persons, by pretending that his invention is more than what it really is, or different from its ostensible objects, that the patentee is required to distinguish his invention in his specification.

13. Claims 1-26 and 28-34 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a Nicotiana host cell having reduced protease activity by sense or antisense suppression of expression of a nucleotide having the nucleotide sequence of SEQ ID NO: 3 or 4 and methods of making, does not reasonably provide enablement for any host cell comprising one or more polynucleotides wherein said polynucleotides encode a genetic element capable of reducing any protease activity in a host cell or fluids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant teaches suppression by co-suppression or antisense an endogenous subtilisin in *Nicotiana benthamiana* using the homologous nucleotide sequence at pages 48-49 of the specification.

Applicant does not teach expression of protease inhibitors, or inhibition of other proteases in other plant or host cells as broadly claimed.

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicant has provided limited guidance on how to make and use the invention as broadly claimed, only exemplifying inhibition of an endogenous protease in *Nicotiana benthamiana* using the homologous nucleotide sequence. It is well established in the art that co-suppression and antisense suppression requires an essentially identical polynucleotide sequence to work predictably in plants. The art teaches that constitutive and inducible expression of proteinase inhibitors incurs large fitness cost to a transgenic plant under realistic growing conditions (see Zavala *et al* 2004, Proc. Natl. Acad. Sci. USA 101(6): 1607-1612). The use of the host cell claimed is to produce a protein of interest, which would be difficult if the fitness of the transgenic plant cell was compromised by the express of a proteinase inhibitor or the inhibition of a proteinase. Hence, given Applicants' limited guidance, the nature of the invention, the unpredictability of the art and the breadth of the claims, it would have required one of skill in the art at the time of Applicant's invention to make and use transformed host

cells with reduced protease activity capable of expressing a protein of interest that is non-native to the host cell as broadly claimed. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970) which teaches "That paragraph (35 USC § 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.".

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-9, 11-14, 17-19, 21, 23-26 are 28-34 rejected under 35 U.S.C. § 102(e) as being anticipated by Gruis *et al,* U.S. Patent 6,855,871 B1 issued 15 February 2006, filed 21 August 2001, and claiming benefit of U.S. Provisional Application 60/226,804, filed 21 August 2000.

Gruis *et al* disclose a plant host cell comprising one or more polynucleotides encoding a protein of interest and a genetic element capable of reducing a protease activity in a host cell at claim 10. Gruis *et al* disclose that the protein of interest includes human growth hormone, which would be non-native to the plant host cell at column 8, 2nd paragraph. Gruis *et al* disclose that the "genetic element capable of reducing a protease activity in a host cell" can be by antisense suppression or sense suppression (claim 1) or by expression of a specific protein processing protease inhibitor (paragraph spanning columns 4-5). Gruis *et al* disclose that subtilisin-type proteases and other serine proteases can be reduced in a transformed plant cell using the disclosed method at column 4, lines 46-60. Gruis *et al* disclose isolation of the polypeptide of interest using methods available in the art at column 6, lines 36-43. Gruis *et al* disclose that the sequences encoding the polypeptide of interest as well as the sense suppression and antisense suppression nucleotide sequences can be linked to join two polypeptide-coding regions at column 15, 2nd paragraph. Hence, Gruis *et al* have previously disclosed all of the claim limitations.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 15-16, 20 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gruis *et al,* U.S. Patent 6,855,871 B1 issued 15 February 2006, filed

21 August 2001, and claiming benefit of U.S. Provisional Application 60/226,804, filed 21 August 2000, in view of Baszczynski *et al*, U.S. Patent 5,824,870, and MacFarlane *et al* (2000 Virology 267: 29-35).

The teachings of Gruis *et al* are outlined above.

Gruis *et al* do not teach using an RNA virus vector, the use of a genetic element encoding aprotinin.

MacFarlane *et al* teach using a Tobravirus vector to introduce and express a transgene in a plant.

Baszczynski *et al* disclose expression of aprotinin in a transgenic plant at claim 7.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The scope and contents of the prior art, and the differences between the prior art and the claims at issue are outlined supra.

Applicant states that the problem addressed by the instant invention is inhibition of peptide cleavage of a protein of interest by a protease native to the plant host (page 1, 2nd paragraph of the specification. The prior art (Gruis *et al*) had taught that the major obstacle to improving the accumulation of heterologous recombinant proteins in plants transformed to express such proteins is the presence of proteases, especially non-seed

recombinant proteins. The prior art had taught that the solution to this problem is by altering the activity of protein processing proteases. Baszczynski *et al* had previously expressed the proteinase inhibitor aprotinin in a transgenic plant, and aprotinin was recognized in the art as a protease inhibitor. Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicants' invention to modify the teachings of Gruis *et al* to express aprotinin in a plant as taught by Baszczynski *et al*, especially since aprotinin was recognized in the art as a protease inhibitor and expressible in a plant cell. The use of a Tobravirus vector to express a heterologous protein or a transgene in a plant or plant cell had been previously taught by MacFarlane *et al*. Gruis *et al* teaches that method know in the art can be used to practice the taught invention (columns 18-19). Hence it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicants' invention to modify the teachings of Gruis *et al* to use an RNA viral vector as taught by MacFarlane *et al*. Given the success of Gruis *et al* in reducing protease cleavage of a protein of interest by suppressing expression of an endogenous protease in a plant cell, and the expression of aprotinin in a plant cell by Baszczynski *et al*, one of ordinary skill in the art would have had a reasonable expectation of success.

Conclusion

18. Claim 10 is free of the prior art, which does not appear to teach a genetic element encoding a Nicotianalisin protein.

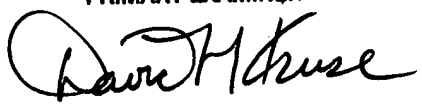
19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached at (571) 272-0975. The central FAX number for official correspondence is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (571) 272-1600.

DAVID H. KRUSE, PH.D.
PRIMARY EXAMINER



David H. Kruse, Ph.D.
13 September 2006

21. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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